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Prostaglandins Evoke a Whole Variety of Responses in the Lung

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Rapid intravenous (IV) injections of the prostaglandin precursor arachidonic acid (AA) increase pulmonary arterial pressure (PAP) and pulmonary vascular resistance (PVR) in a variety of species. It has recently been reported that infusions of AA decrease PAP. The purpose of this report is to contrast responses to bolus injections and infusions of AA in the anesthetized cat. In all experiments rapid IV injections of AA increased PAP and PVR; however, infusions of 68 to 680 μg/min produced variable responses. In 10 of 19 animals, AA infusion decreased PAP and PVR, and this response was enhanced when pulmonary vascular tone was actively increased by vasoconstrictor agents or alveolar hypoxia. In the other nine animals, the predominant response was an increase in PAP and PVR. In all experiments infusions of larger amounts of AA (1.4 to 3.4 mg/min) increased PAP. Both pressor and depressor responses to AA were inhibited by meclofenamate. This study shows that infusion of small amounts of AA dilates or constricts the pulmonary vascular bed. In contrast, infusion of larger amounts of AA always causes vasoconstriction. These data suggest that at low infusion rates, PGI_2, which is a vasodilator, is the predominant metabolite formed from AA in some animals. However, at higher concentrations, the production of constrictor products predominates. These experiments also suggest that the products formed and the response observed may be dependent on a number of factors including the amount of tone present in the pulmonary vascular bed.

Introduction

In most organ systems including the lung, arachidonic acid (5, 8, 11, 14-eicosatetraenoic acid) is converted into the endoperoxide intermediates PGG_2 and PGH_2 by a microsomal cyclooxygenase (*1-3*). The endoperoxide intermediates (PGG_2 and PGH_2) are then converted by terminal enzymes into primary prostaglandins (PG), thromboxane A_2 (TXA_2) or prostacyclin, PGI_2 (*2-9*). The distribution and activity of terminal enzymes determine the pattern of products formed from endoperoxide intermediates in an organ (*9-11*). Many reports indicate that the endoperoxide intermediate, endoperoxide analogs, PGE_2, $PGF_{2\alpha}$, and PGD_2 all increase pulmonary vascular resistance in a variety of species (*10, 12-17*). In contrast, PGE_2 has dilator activity in the pulmonary circulation of fetal and neonatal animals (*18*). The pulmonary vascular effects of TXA_2 are uncertain, but this labile substance has potent smooth muscle stimulating and platelet aggregating activity and its breakdown product, TXB_2, has modest pressor activity in the pulmonary vascular bed (*7, 19*). In contrast to the effects of PGH_2, PGE_2, PGD_2, $PGF_{2\alpha}$, and TXB_2, the newly discovered metabolite of arachidonic acid metabolism, PGI_2 has pulmonary vasodilator activity (*7, 19*). However, the effects of arachidonic acid on the pulmonary vascular bed are unclear. Arachidonic acid has been shown to increase pulmonary vascular resistance in a number of species when injected as a bolus and to contract isolated segments of pulmonary artery (*10, 12, 13, 20-22*). These responses are blocked by indomethacin suggesting that in the lung arachidonate, when administered as a bolus is converted to substances that have pulmonary vasoconstrictor and bronchoconstrictor activity (10, 12, 13, 21, 22). It has, however, recently been reported that arachidonic acid has depressor activity in the pulmonary circulation when the prostaglandin precursor is infused (*12*). It has also been recently shown that the newly discovered bicyclic prostaglandin PGI_2 dilates that

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feline and canine pulmonary vascular beds (*23, 24*). The purpose of the present report is to compare responses to primary prostaglandins (PGE_2, $PGF_{2\alpha}$, and PGD_2), arachidonic acid, and prostacyclin in the canine pulmonary vascular bed and the airways.

Methods

The pulmonary vascular effects of primary prostaglandins, arachidonic acid and prostacyclin were investigated in mongrel dogs unselected as to sex weighing 14.2-24.5 kg. The dogs were anesthetized with pentobarbital sodium (30 mg/kg, IV) and strapped to a Philips heart table in the supine position. A 6F Edslab thermal dilution catheter was passed into the main pulmonary artery from the external jugular vein under fluoroscopic guidance (Philips image intensifier). Pulmonary arterial pressure was measured from the distal port on the Edslab catheter. A 7F Teflon catheter was passed into the left atrium transseptally and large bore catheters were positioned in the aorta from a femoral artery and in a femoral vein. Cardiac output was determined with an Edwards thermal dilution computer, model 9500, after injection of 5 ml of 5% dextrose solution (cooled to 0°C) into the superior vena cava (proximal port on the Edslab catheter). Values for cardiac output averaged 120 ml/kg per min and compared favorably with cardiac outputs determined by the indicator-dilution technique in this laboratory. The dogs breathed room air, or room air enriched with O_2, spontaneously through a cuffed endotracheal tube.

In dogs in which constant flow perfusion of the left lower lobe was employed, a specially designed 20F double-lumen balloon catheter was introduced through a jugular vein into the arterial branch of the left lower lung lobe under fluoroscopic guidance. A 1.5 mm Teflon catheter with its tip positioned about 2 cm distal to the tip of the perfusion catheter was used to monitor perfusion pressure in the lobar artery. Catheters with side holes near the tip were passed into the main pulmonary artery and femoral artery and transseptally into a small intrapulmonary vein and the left atrium. Precautions were taken to ensure that pressure measurements were made without wedging in veins 2-3 mm in diameter. Briefly, a 0.9 mm Teflon catheter with two side holes near the tip was passed through a 3 mm Teflon catheter that previously had been wedged in a small intrapulmonary vein. The 0.9 mm catheter was then withdrawn 1-3 cm from the wedge position until pressure dropped abruptly. The 0.9 mm catheter was fixed in place with a Cope adaptor after the larger catheter had been withdrawn to the left atrium. These methods have been described in detail previously and a diagram of the catheterization procedure is shown in Figure 1 (*12, 14*). All vascular pressures were measured with Statham P23D transducers zeroed at the level of the middle of the right atrium, and mean pressures were recorded on an oscilloscopic recorder (model DR-12, Electronics for Medicine). After all catheters had been positioned and the dogs heparinized (500 U/kg, IV) the balloon on the perfusion catheter was distended with 2-4 ml of 50% sodium diatrizoate (Hypaque Winthrop) until pressure in the lobar artery and small vein decreased to near left atrial pressure. The vascularly isolated left lower lobe then was perfused with a Sarns roller pump (model 3500) with blood withdrawn from the right atrium. The pumping rate was adjusted so that mean pressure in the perfused lobar artery approximated mean pressure in the main pulmonary artery and thereafter was not changed during the experiment. The pumping rate averaged 260 ml/min. These dogs spontaneously breathed room air or room air enriched with O_2 through a cuffed endotracheal tube.

In experiments in which the effects of the analogue on airway pressure were evaluated, the dogs were

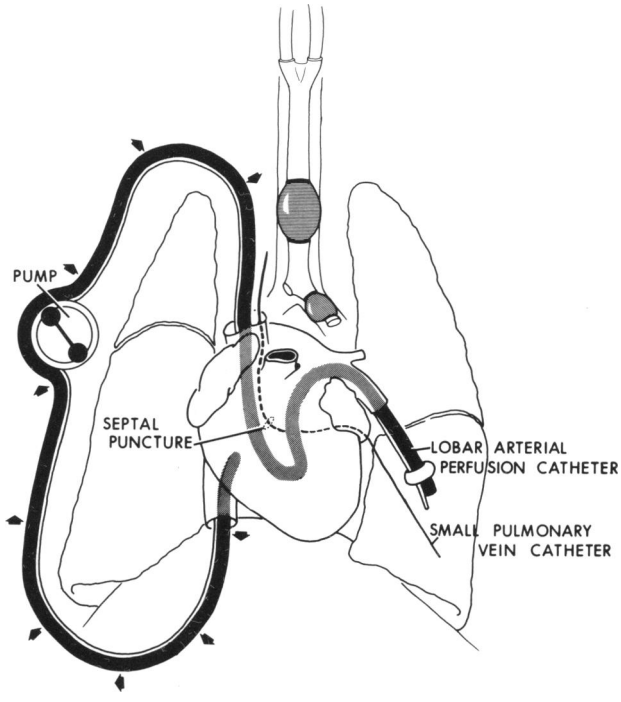

FIGURE 1. Diagram showing catheterization procedure in the dog. A specially designed 20F balloon catheter is passed into the artery of the lower left lobe and the lung is autoperfused with the blood withdrawn from the right atrium. Vascular pressures are measured in the perfused lobar artery, a small pulmonary lobar vein, and the left atrium and in the main pulmonary artery and the aorta. The Carlen's endobronchial catheter permits the left lower and right lungs to be ventilated separately.

intubated with a Carlen's endobronchial divider (no. 39) and the left lower lobe and right lungs were ventilated separately with a Harvard dual-cylinder respiratory (model 618) at a rate of 20 cycles/min with stroke volumes of 110 ml/min for the left lower lobe and 280 ml/min for the right lungs. The dogs received succinylcholine chloride (Anectine, Burroughs Wellcome), 2.5 mg/kg, IV, to paralyze ventilation. Translobar airway pressure was measured with a Statham differential transducer (PM5) bridged between the left side of the endobronchial divider and the pleural space and was recorded on the Electronics for Medicine recorder.

For studies on lung function, mongrel dogs, unselected as to sex, weighing from 14.2-18.5 kg, were anesthetized with chloralose (50 mg/kg) and urethane (500 mg/kg) administered intravenously. Polyethylene catheters were advanced from the femoral artery and vein for the recording of aortic pressure (P_{Ao}) and the administration of drugs, respectively. A 6F Edslab double lumen thermodilution catheter (Edwards Laboratories) was passed from the external jugular vein into the main pulmonary artery under fluoroscopic guidance. Pulmonary arterial pressure (P_{PA}) was measured from the distal port of this catheter. In some experiments, left ventricular end-diastolic pressure was measured through a Cordis pig-tail catheter advanced from a femoral artery or, alternately, left atrial pressure was measured directly through a 7F Teflon catheter positioned transseptally in the left atrium. Cardiac output was determined with an Edwards Laboratories Thermal Dilution Computer, Model 9500A. All vascular pressures were measured with Statham P23BB or P23AC transducers zeroed at atrial level. Mean pressures were obtained from the pulsatile signal by electrical averaging.

The dogs were ventilated with a Harvard ventilator through a short tracheal cannula (2-3 cm diameter) introduced by tracheostomy. Transpulmonary pressure P_{TP} was measured by a Statham PM5E differential transducer interposed between the tracheal cannula and a Harvard pleural cannula inserted through the chest wall at the 4th or 5th intercostal space. Pneumothorax was adjusted to 10-20 ml immediately after introduction of the pleural cannula. Air flow $\dot{V}$ was measured with a Fleisch No. 1 pneumotachograph heated above body temperature and coupled to a Grass PT5A differential transducer. P_{TP} and $\dot{V}$ signals were processed by a Hewlett-Packard 8816A Respiratory Analyzer which provided, on line, volume V, dynamic compliance C_{dyn} and resistance of the lung R_L. C_{dyn} was computed between points of zero flow by dividing the volume of each breath by the difference between end-inspiratory and end-expiratory P_{TP}. R_L was computed at early expiration by the method of Mead and Whittenberger (*25*) in which instantaneous resistive pressure was divided by instantaneous flow. Resistive pressure is derived by subtracting the ratio of volume to computed compliance from P_{TP}. Percent CO_2 in end-tidal air was monitored periodically with a Beckman LB-2 medical gas analyzer connected to a tap between the respirator and the pneumotachograph. P_{TP}, $\dot{V}$, V, R_L, C_{dyn} and vascular pressures were recorded on a Grass model 7C 8-channel recorder. The preparation used to investigate the effects of the prostaglandins on lung function in the intact chest dog is illustrated in Figure 2, and this preparation has been reported on previously (*21*). The animals were heparinized with sodium heparin (Upjohn), 500 Units/kg iv and spontaneous breathing was arrested with succinylcholine chloride (Anectine, Burroughs Wellcome), 30-40 mg IV, repeated as needed. After neuromuscular blockade, increments of anesthetic were given as needed. Minute volume was set with tidal volume at 12 ml/kg and the rate sufficient to maintain end-tidal CO_2 near 5% and blood gases in a normal range. A lung volume history was established by hyperinflating the dog to three

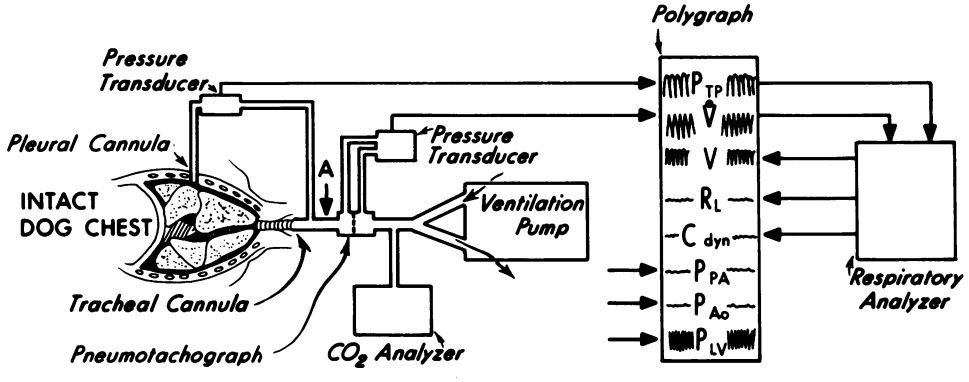

FIGURE 2. Schematic diagram of the procedure used to evaluate the effects of the prostanoids on lung function in the intact chest dog.

times the tidal volume 3 min prior to each administration of test agent into the superior vena cava (SVC).

Arachidonic acid (NuChek) 99% pure and indomethacin (Merck) were freshly prepared as sodium salts: arachidonic acid in 10% ethanol in 100 mM sodium carbonate and indomethacin in 100 *mM* sodium carbonate in normal saline. Prostaglandins D_2, E_2, and $F_{2\alpha}$ and the PGH_2 analog (Upjohn) were dissolved in absolute ethanol and stored at −20°C. Working solutions were freshly prepared in saline. PGI_2 was prepared in 20*mM* Tris buffer, pH 8.5, and was stored in a freezer.

All values are expressed as the mean ± standard error of the mean unless otherwise indicated. Tests of significance for group and paired comparisons were done according to standard statistical methods (*25*). A p value less than 0.05 was considered significant.

Results

The pathway for synthesis of primary prostaglandins (PGD_2, PGE_2, and $PGF_{2\alpha}$), thromboxane A_2 (TXA_2), and prostacyclin (PGI_2) in the lung is illustrated in Figure 3. The fatty acid precursor, arachidonic acid, is converted into endoperoxide intermediates by a microsomal cyclooxygenase. The endoperoxide intermediates are then converted by terminal enzymes into prostaglandins, TXA_2 or prostacyclin. Alternatively, the endoperoxides may be broken down to 12-hydroxyheptadecatrienoic acid (HHT) and malondialdehyde (MDA), which have little reported biologic activity. Although the endogenous precursor is derived from the breakdown of phospholipids in cell membranes, exogenous arachidonic can also serve as substrate for the cyclooxygenase. The effects of exogenously administered arachidonic acid on the pulmonary vascular bed perfused at constant flow are illustrated in Figure 4. Injection of arachidonic acid, 3 mg, as a rapid bolus into the perfused lobar artery produced a rapid increase in lobar arterial and small vein pressures but had no effect on left atrial pressure. The effects of arachidonic acid on lobar arterial and venous pressure were dose-related in the range of doses of 0.1-3 mg and at doses of 1-3 mg aortic pressure was decreased.

The pressor activities of arachidonic acid, PGE_2, $PGF_{2\alpha}$, and a stable endoperoxide (PGH_2) analog in the pulmonary vascular bed under conditions of controlled flow are compared in Figure 5. $PGF_{2\alpha}$ is about 10-fold more potent than PGE_2, which in turn is about 10-20 times more active than arachidonic acid. The stable endoperoxide analog is about 10-fold more active than $PGF_{2\alpha}$. Although not shown on

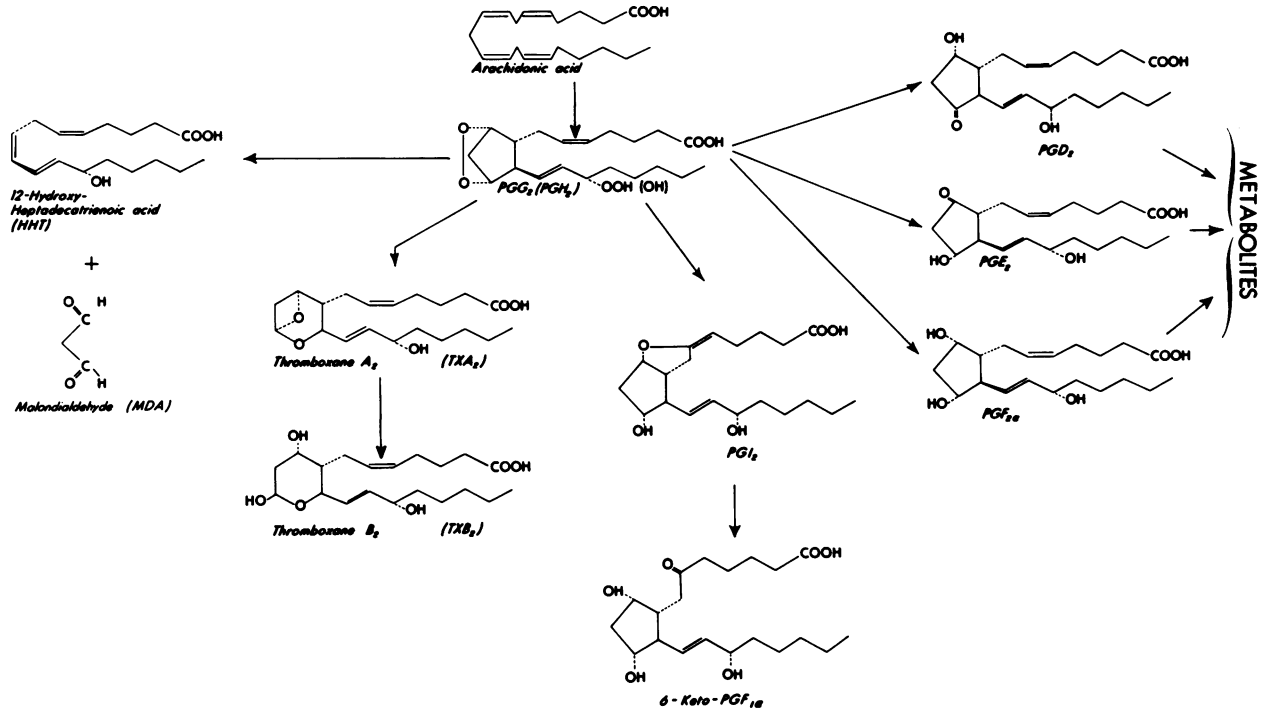

FIGURE 3. Diagram showing the pathway for biosynthesis of PGD_2, $PGF_{2\alpha}$, PGE_2, thromboxane A_2, and PGI_2 in the lung.

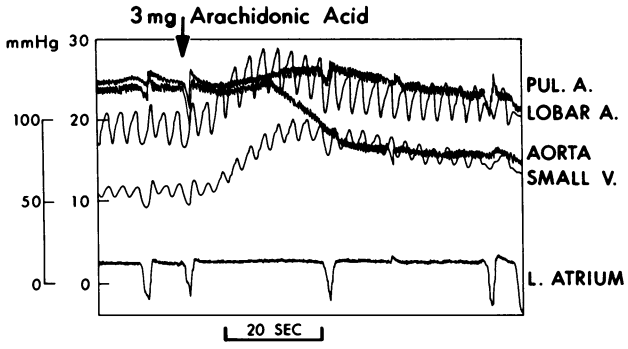

FIGURE 4. Records from an experiment in the intact chest dog, showing the effects of arachidonic acid (3 mg) injected into the lobar artery on mean pressures in the main pulmonary artery (Pul. A), the lobar artery (lobar A.), the Aorta, the small intrapulmonary vein (small v.) and the left atrium (L atrium). Blood flow to the left lower lobe was maintained constant with a pump.

Figure 5, the pressor activities of $PGF_{2\alpha}$ and PGD_2 are very similar. In addition to increasing lobar arterial and venous pressures, arachidonic acid increases translobar airway pressure indicating that the prostaglandin precursor is converted into substances that have bronchomotor activity in the dog (Fig. 6). The airway effects of arachidonic acid were studied further using the procedure illustrated in Figure 2. The effects of arachidonic acid on the airways are depicted in Figure 7. Rapid bolus injection of 10 mg of the prostaglandin precursor into the superior vena cava increased transpulmonary pressure to 200% of control value. The response attained a peak within 20 sec and transpulmonary pressure gradually returned toward control value. The rise in transpulmonary pressure was accompanied by a transient rise in lung resistance and a greater and more sustained decrease in dynamic compliance. The effects of arachidonic acid on lung function were dose-related and hyperinflation of the lung to total lung capacity 10-15 min after administration of the prostaglandin precursor usually returned lung resistance and dynamic compliance to control levels. The effects of arachidonic acid, PGD_2, and $PGF_{2\alpha}$ on lung function in the intact dog are compared in Figure 8. All three substances increased pulmonary arterial pressure and lung resistance and decreased dynamic compliance in a dose-dependent manner. PGD_2 was three times more active than $PGF_{2\alpha}$ in increasing lung resistance and decreasing lung compliance whereas both prostaglandins were more than 1000-fold more active than arachidonic acid. PGE_2 had only small airways effects in range of doses of 1-30 μg. The stable endoperoxide analog and PGD_2 had similar effects on the airways in the intact dog.

The effects of indomethacin on pulmonary vascular, airway and systemic vascular responses to arachidonic acid are illustrated in Figure 9. The increases in transpulmonary pressure, pulmonary arterial pressure and aortic pressure were abolished

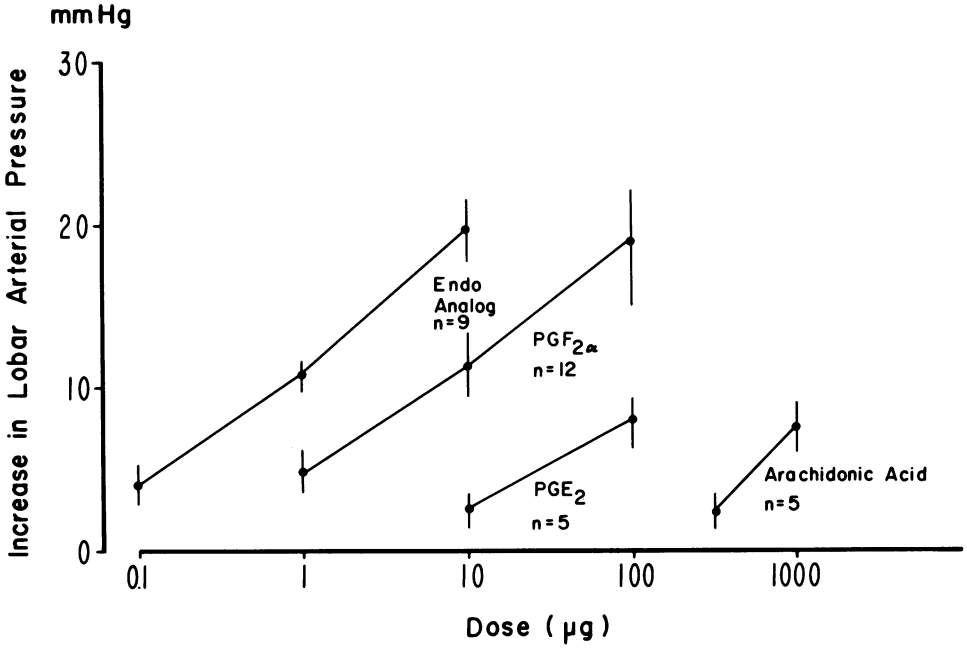

FIGURE 5. Dose-response curves comparing increases in lobar arterial pressure in response to graded doses of an endoperoxide (PGH_2) analog, $PGF_{2\alpha}$, PGE_2, and arachidonic acid. *n* indicates the number of animals studied, and blood flow to the left lower lobe was maintained constant with a pump.

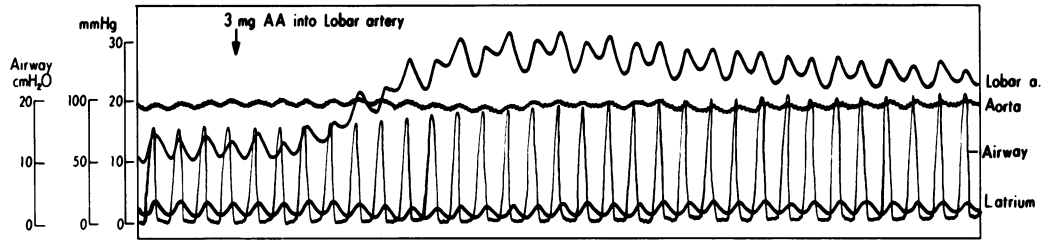

FIGURE 6. Tracings from an experiment illustrating the effects of injection of arachidonic acid (3 mg) into the perfused lobar artery on mean vascular pressures in the lobar artery (lobar a.), the aorta, the left atrium (L atrium), and on translobar airway pressure. Blood flow to left lower lobe was maintained constant with a pump and the left lower lobe was ventilated separately using a Carlen's endobronchial divider.

5-10 min after administration of indomethacin 2.5-5 mg/kg IV. The pulmonary vascular effects of the newly discovered bicyclic prostaglandin, prostacyclin (PGI_2) are summarized in Table 1. PGI_2 produced a small but significant reduction in lobar arterial and small vein pressures when injected as a bolus in doses of 1-10 μg into the perfused lobar artery. Although responses to PGI_2 were small under resting conditions when tone in the pulmonary vascular bed was minimal, decreases in lobar arterial and venous

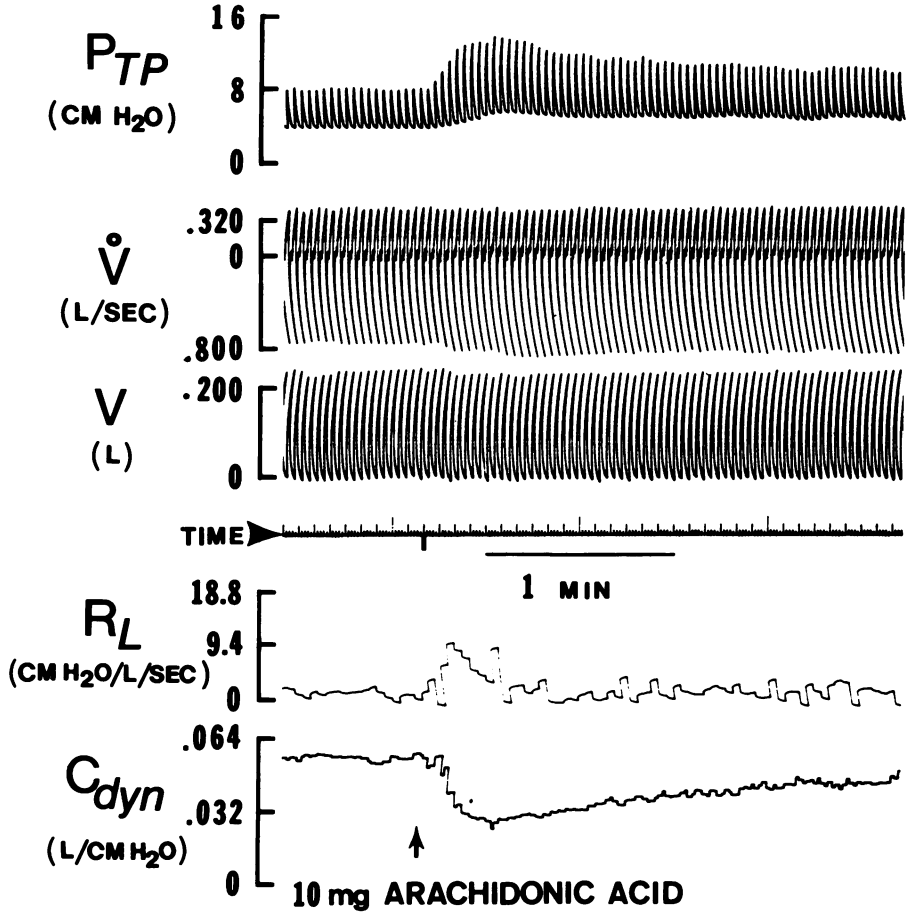

FIGURE 7. Record from an experiment illustrating the effects of arachidonic acid (10 mg) on transpulmonary pressure P_{TP} (inspiration up), air flow $\dot{V}$, (inspiration upward from zero, expiration downward), tidal volume V, lung resistance R_L, and dynamic compliance C_{dyn} in the intact chest dog. Mean pulmonary arterial pressure P_{PA} was increased and mean aortic pressure P_{Ao} (not shown in this figure) was decreased. Injection was made as a bolus into the superior vena cava at the point indicated.

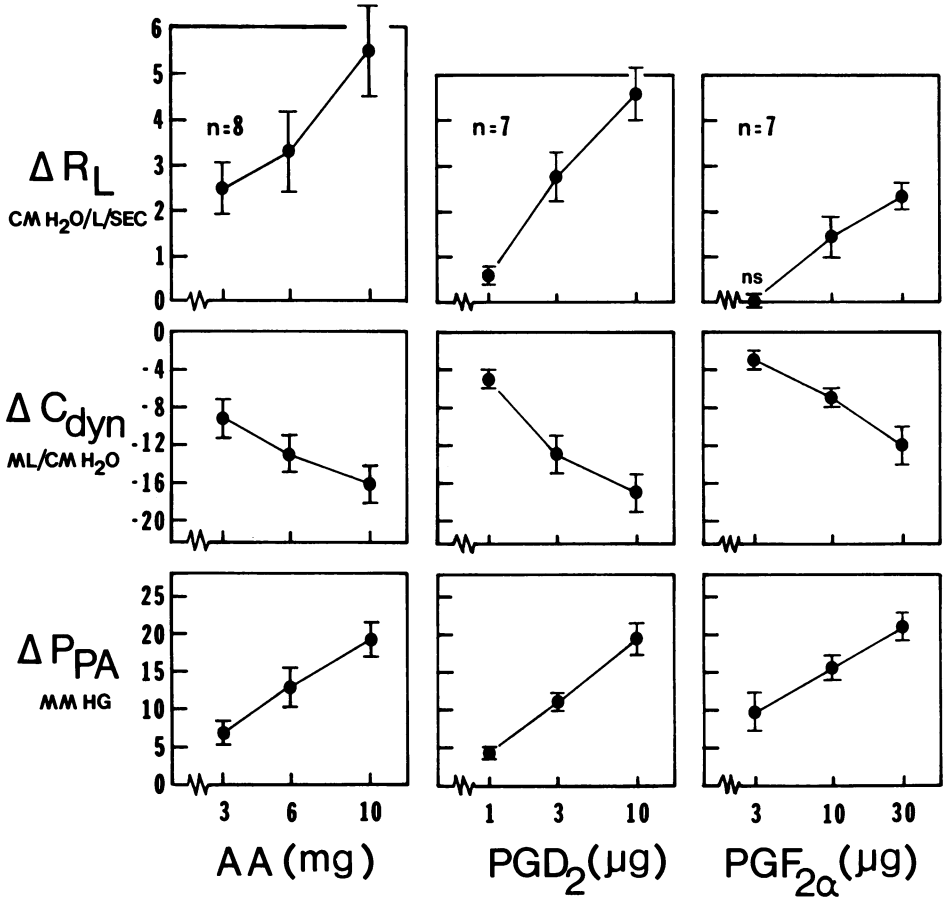

FIGURE 8. Dose-response curves comparing effects of arachidonic acid (AA), PGD_2, and $PGF_{2\alpha}$ on lung resistance R_L, dynamic compliance C_{dyn}, and pulmonary arterial pressure P_{PA} in intact chest dog.

pressures were substantial when pulmonary vascular resistance was actively increased (Table 1). In preliminary studies PGI_2 had little effect on the airways in the cat and dog under resting conditions but decreased transpulmonary pressure when bronchomotor tone was enhanced.

Discussion

Results of the present study show that when injected as a bolus the prostaglandin precursor, arachidonic acid, increases lobar arterial and small vein pressures in the intact dog. Inasmuch as pulmo-

Table 1. Pulmonary vasodilator effects on PGI_2 under resting conditions and when pulmonary vascular resistance is enhanced by infusion of an endoperoxide analog.

	Pressure ± SE, mm Hg			
	Lobar artery	Small vein	Left atrium	Aorta
Control	15.9 ± 0.8	10.5 ± 0.6	1.8 ± 0.4	120 ± 5
PGI_2, 1-10 μg	14.0 ± 1.0[a]	9.2 ± 0.6[a]	1.8 ± 0.4	99 ± 8[a]
Control + infusion of 11,9-PGH_2 analog, 1-5 μg/min	31.5 ± 1.3	21.4 ± 1.0	1.7 ± 0.2	125 ± 1.5
PGI_2, 1-10 μg, + infusion of 11,9-PGH_2 analog, 1-5 μg/min; $n = 6$	25.1 ± 2.6[a]	17.1 ± 1.3[a]	1.6 ± 0.2	106 ± 5.2[a]

[a] $p < 0.05$ when compared to corresponding control (paired comparison).

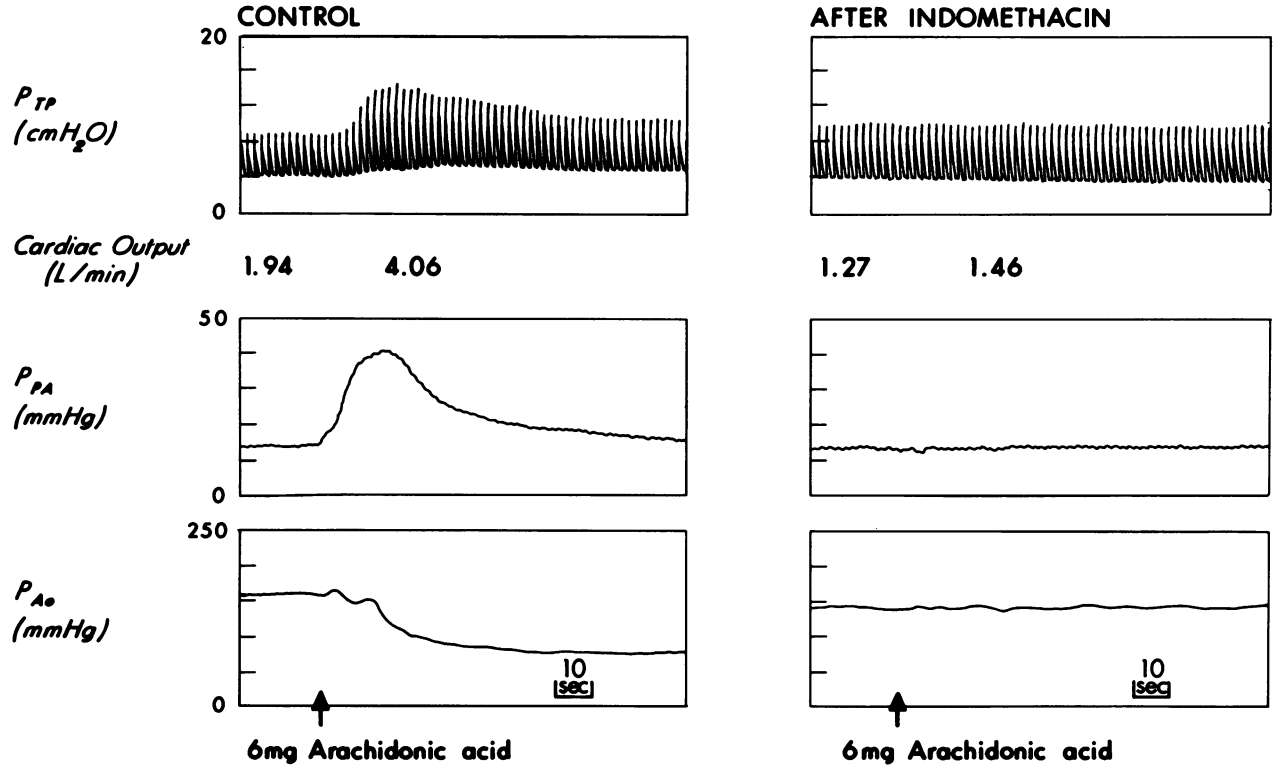

FIGURE 9. Records from an experiment illustrating the effects of arachidonic acid (6 mg) on transpulmonary pressure P_{TP}, mean pulmonary arterial pressure P_{PA} and mean aortic pressure P_{Ao} (*A*) before and (*B*) 20 min after a slow intravenous infusion of indomethacin, 2.5 mg/kg. At the arrows, arachidonic acid was injected as a bolus into the superior vera cava. Cardiac output in liters per minute was measured by the thermal dilution technique at the peak of the response.

nary blood flow was held constant and left atrial pressure was unchanged, the rise in lobar arterial pressure reflects an increase in pulmonary vascular resistance. The rise in small vein pressure and in pressure gradient from the lobar artery to the small vein suggests that arachidonic acid increases pulmonary vascular resistance by constricting small intrapulmonary veins and upstream segments believed to be small arteries (*12*). The primary prostaglandins (PGE_2, PDG_2, and $PGF_{2\alpha}$) as well as PGH_2 and a stable PGH_2 analog, all increase pulmonary vascular resistance in the dog and cat (*10, 12-17, 22*). Arachidonic acid also increased transpulmonary pressure when the lung was ventilated at constant volume with a positive pressure ventilator (*12*). In experiments in which the effects of arachidonic acid on lung function were further investigated, the increase in transpulmonary pressure was associated with a transient rise in lung resistance and a sustained fall in dynamic compliance (*21*). The endoperoxide analog, $PGF_{2\alpha}$, and PGD_2 all increased lung resistance and decreased dynamic compliance and in this regard were similar to but much more potent than arachidonic acid (*17, 21, 26*). The effects of PGE_2 on the pulmonary vascular bed and on the airways were modest when this substance was injected in the same doses as PGD_2 or $PGF_{2\alpha}$ (*12, 13, 16, 21*). Pulmonary vasoconstrictor, bronchoconstrictor and systemic vasodepressor responses to arachidonic acid were blocked after administration of indomethacin, a cyclooxygenase inhibitor (*10-13, 21*). These data suggest that the effects of arachidonic acid on the airways, pulmonary and peripheral vascular beds is due to the conversion of the substrate into vasoactive and bronchoactive metabolites in the cyclooxygenase pathway. The pulmonary vasoconstrictor response to arachidonic acid is associated with increased synthesis of E and F "like" prostaglandins, however; it is not known if PGD_2 or TXB_2 are produced by the lung in the intact dog (*12*). The effects of arachidonic acid on the pulmonary vascular bed were not dependent on the presence of platelets or other formed elements in that the response to arachidonic acid was not diminished when the lung was perfused with a dextran solution (*12*). These findings suggest that the substrate is converted to vasoactive substances by the lung itself and that platelet aggregation or release of vasoactive products from the

platelets play little or no role in this response (*12*).

In contrast to the pressor effects of $PGF_{2\alpha}$, PGD_2, and PGE_2 or the PGH_2 analog which may mimic the effects of TXA_2 on the pulmonary vascular bed, the newly discovered bicyclic prostaglandin, PGI_2, had vasodilator activity in the pulmonary vascular bed (*23, 24*). The pulmonary vasodilator effects of PGI_2 were modest under resting conditions but were greatly enhanced when pulmonary vascular resistance was increased actively by infusion of a vasoconstrictor substance (*23*). Although PGI_2 had vasodilator activity, arachidonic acid when administered as a bolus, consistently increased pulmonary vascular resistance in the intact dog and cat and in the isolated dog lung (*10, 12, 13, 21, 22*). These results suggest that under physiologic conditions in the intact state, the predominant products formed in the lungs when arachidonate is injected as a bolus are vasoconstrictor in nature. Alternatively, it is possible that both vasoconstrictor and vasodilator metabolites are formed but that the activity of the vasoconstrictors overshadows the action of any simultaneously formed "PGI_2-like" substances. It has been reported that PGI_2 is the predominant metabolite formed from arachidonic acid and endoperoxide intermediates in vascular tissue (*5, 8, 27*). Indeed, we have observed in some animals that slow infusions of arachidonic acid decrease pulmonary vascular resistance in the intact dog and cat. The explanation for the divergent responses to rapidly injected arachidonic acid and slowly infused arachidonic acid are uncertain at the present time. It is however possible that, when excessive amounts of substrate are converted to PGH_2, the endothelial prostacyclin synthetase may be overwhelmed and the endoperoxide may isomerize to PGD_2 and PGE_2 or be reduced to $PGF_{2\alpha}$.

We have reported that administration of cyclooxygenase inhibitors such as indomethacin and meclofenamate result in a slow gradual increase in pulmonary vascular resistance in the intact dog (*28*). It has been shown that a PGI_2-like substance is continually released by the lung (*6*). We have, therefore, suggested that under resting conditions, the pulmonary vascular bed is maintained in a dilated state by production of a vasodilator product in the cyclooxygenase pathway (*28*). Recent evidence suggests that this vasodilator product in the cyclooxygenase pathway is a PGI_2-like substance (*6, 23, 24*). It would therefore be of interest to ascertain if industrial pollutants such as NO_2 or SO_2 have adverse effects on enzymes such as cyclooxygenase or prostacyclin synthetase which function to synthesize PGI_2 which serves to maintain the pulmonary vascular bed in a dilated state under resting conditions.

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